UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ROBERT STUART COFFIN and DAVID SEYMOUR LATCHMAN

Appeal No. 2007-1037
Application No. 09/762,098

ON BRIEF

Before ADAMS, GREEN, and LEBOVITZ, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 34-46, which are all the claims pending in the application.

Claim 34[1] is illustrative of the subject matter on appeal and is reproduced below:

34. A process for propagating a mutant herpes simplex virus (HSV) comprising:
(a) a mutation in its endogenous VP16 gene wherein the mutation reduces or abolishes the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein; and
(b) a heterologous gene;
which process comprises infecting a cell line with the mutant herpes virus and culturing the cell line,

[1] Claims 35-46 depend directly or indirectly from claim 34.

wherein the cell line comprises a nucleic acid sequence from a non-HSV herpes virus encoding a functional equivalent of the HSV VP16 polypeptide operably linked to a control sequence permitting expression of the polypeptide in said cell line and wherein the nucleic acid sequence (i) complements the endogenous gene and (ii) does not undergo homologous recombination with the endogenous gene.

The references relied upon by the examiner are:

Speck et al. (Speck) WO 96/04395 Feb. 15, 1996

Moriuchi et al. (Moriuchi), "Varicella-Zoster Virus Open Reading Frame 10 Protein, the Herpes Simplex Virus VP16 Homolog, Transactivates Herpesvirus Immediate-Early Gene Promoters," J. Virology, Vol. 67, No. 5, pp. 2739-2746 (1993)

Purewal et al. (Purewal), "Equid Herpesviruses 1 and 4 Encode Functional Homologs of the Herpes Simplex Virus Type 1 Virion Transactivator Protein, VP16," Virology, Vol. 198, No. 385-389 (1994)

GROUND OF REJECTION

Claims 34-46 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Speck, Moriuchi and Purewal.

We reverse.

DISCUSSION

Claim Interpretation:

Claim 34 is drawn to a process for propagating a mutant herpes simplex virus (HSV). The process comprises infecting a cell line with the mutant herpes virus and culturing the cell line. We note however, that claim 34 places limitations on both the mutant HSV and the cell line.

According to claim 34 the mutant HSV comprises (a) a mutation in its endogenous VP16 gene that reduces or abolishes the ability of the protein

encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein; and (b) a heterologous gene.

As to the cell line, claim 34 requires that the cell line comprise a nucleic acid sequence from a non-HSV herpes virus encoding a functional equivalent of the HSV VP16 polypeptide operably linked to a control sequence permitting expression of the polypeptide in the cell line. Claim 34 requires that the non-HSV VP16 equivalent nucleic acid sequence (i) complements the endogenous gene and (ii) does not undergo homologous recombination with the endogenous gene.

Obviousness:

Claims 34-46 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Speck, Moriuchi, and Purewal.

According to the examiner (Answer, page 3), Speck teaches a mutated herpesvirus, wherein the mutation is to, inter alia, impair VP16 and a method of making and using the mutant as a recombinant HSV vector. In addition, the examiner finds that this recombinant HSV "vector further comprises a heterologous sequence encoding a therapeutic polypeptide." Id. More specifically, Speck teaches

> [a] mutant herpesvirus that can be used as a recombinant virus vector compris[ing] (a) a mutation such that the mutant virus has a reduced ability in comparison with a parent type to cause lysis of an infected cell, and (b) an inactivating mutation in a gene essential for the production of infectious virus. An example is a HSV1 mutant lacking the essential glycoprotein gH gene and having a mutation impairing the function of gene product VP16. A heterologous gene can be carried at the site of the inactivated essential gene, e.g., a gene suitable for administering gene therapy.

Speck, abstract. According to Speck (page 3), such a mutation in the VP16 gene of herpes simplex virus type 1 is effective to reduce or substantially remove, the transinducing properties of the protein encoded by that gene while retaining its structural role. Thus, Speck teaches a mutant HSV within the scope of appellants' claimed invention.

Speck also teaches a process for propagating the mutant HSV. Speck, page 9. The process comprises infecting a cell line with the mutant herpes virus and culturing the cell line. Id. As to the cell line, Speck teaches that the "mutant virus can be grown on a complementing cell line . . . [which] has been made recombinant by insertion of DNA encoding a product that complements the inactivating mutation (b) mentioned above in an essential viral gene . . . ." Speck, page 6. Speck also teaches that "it can be convenient to make the complementing cell line complement both of the mutations (a) and (b)." Id.

Speck, however, prefers "not to complement a mutation in the VP16 gene in the complementing cell line . . . ." Speck, page 7. As Speck explains (id.), the intent is to produce mutant virus that is free from replication-competent virus. Since, the mutant VP16 gene product forms part of the virion (id.), one would expect that by complementing the mutant virus with VP16 a revertant virus will be obtained – e.g., one that is replication-competent. As appellants explain (Brief, page 10), there are two reasons why a complementing cell line that expresses VP16 cannot be used for propagation of the mutant virus. First, including "a wild-type copy of the VP16 gene in a cell line used for virus growth would lead to the

generation of a revertant HSV containing wild-type VP16 by homologous recombination." Brief, page 10. Second,

> wild-type VP16 protein expressed in the cell line would be incorporated into new HSV virions. Hence, a vector stock produced on such a cell line would include HSV virions containing fully functional VP16 protein. These fully functional VP16 proteins would, on infection of a cell, be released and serve to transactivate IE [(immediate early)] gene expression just as the transactivating mutation was intended to prevent . . . .

What is absent is Speck is a teaching of a non-HSV herpes virus nucleic acid encoding a functional equivalent of the HSV VP16 polypeptide that complements the endogenous gene, yet would not have the same disadvantages expected with the use of the native VP16 gene as explained above.

In this regard, the examiner relies on Moriuchi to "teach that a HSV VP16 counterpart, VZV open reading frame 10 (ORF10) is able to complement the VP16 mutant HSV in 1814 [sic]." Answer, page 4. According to the examiner Moriuchi demonstrate that VZV ORF10 is able to complement the VP16 mutant HSV in1814[2] in a cell line that expresses VZV ORF10 under the control of an inducible promoter. Id. More specifically, Moriuchi teaches the use of a cell line comprising a non-HSV herpes virus nucleic acid encoding a functional equivalent[3] of the HSV VP16 polypeptide to complement a mutant HSV that comprises a mutation in its endogenous VP16 gene. Moriuchi, Abstract, page 2739, column 2, and page 2745, column 1. Thus, the examiner has provided evidence to establish that VZV ORF10 and VP16 are functional equivalents. Where, as here, the prior art recognizes two components to be

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[2] According to Moriuchi (abstract), HSV "in1814 lacks the transactivating function of VP16 . . . ."

[3] E.g., one that acts nearly as effectively as HSV-1 VP16. Moriuchi, page 2745, column 1.

equivalent, an express suggestion to substitute one for another need not be present in order to render such substitution obvious. In re Fout, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982).

Moriuchi, however, fails to teach that VZV ORF10 will not suffer the same deficiencies as would be expected in a recombinant cell line comprising the endogenous VP16 gene.[4] Therefore, while it may have been obvious to try using VZV ORF10 in Speck's system, there is no reasonable expectation of success that VZV ORF10 will overcome the expected deficiencies associated with the use of VP16. At best, one would expect that by complementing the mutant virus with VZV ORF10 a revertant virus would be obtained just as would be expected by complementing with VP16. To establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). On this record, the examiner fails to establish that a person of ordinary skill in the art would have had a reasonable expectation of successfully complementing a HSV with a mutant in the VP16 gene with VZV ORF10, without obtaining revertant virus.

Accordingly, it is our opinion that Moriuchi fails to make up for the deficiencies in Speck.

[4] Moriuchi also does not teach a mutant HSV which comprises a heterologous gene.

We also find that Purewal fails to make up for the deficiencies in Speck alone or in combination with Moriuchi. According to the examiner Purewal teaches two other proteins (EHV-1 and EHV-4), which like VZV ORF10, are able to transactivate the HSV-1 immediate early gene. Answer, page 4. However, like Moriuchi, Purewal does not teach that EHV-1, EHV-4, or VZV ORF10 will not suffer the same deficiencies as would be expected in a recombinant cell line comprising the endogenous VP16 gene.[5]

For the foregoing reasons, we disagree with the examiner's assertion that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use "a complementing cell line that express[es] the HSV VP16 counterpart to propagate the HSV VP16 mutant. . . ." Answer, page 4. We disagree with the examiner's rationale (id.) that since Speck teaches that HSV double mutants, which include a mutation in the VP16 gene, are able to grow in a complementing cell line a person of ordinary skill in the art would have been motivated to use a recombinant cell line comprising the VZV ORF10 or EHV-1 gene to complement and grow the defective virus. In our opinion, Speck would lead a person of ordinary skill in the art away from this conclusion. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

[5] In addition, Purewal does not teach a virus that comprises a heterologous gene or that EHV-1 or EHV-4 can be used in a complementing cell line to complement a HSV with a mutation in the VP16 gene.

On reflection, we find that the examiner has failed to meet her burden[6] of providing the evidence necessary to establish a prima facie case of obviousness. If the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly, we reverse the rejection of claims 34-46 under 35 U.S.C. § 103 as being unpatentable over the combination of Speck, Moriuchi and Purewal.

REVERSED

Donald E. Adams
Administrative Patent Judge

Lora M. Green
Administrative Patent Judge

Richard M. Lebovitz
Administrative Patent Judge

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[6] In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

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